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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,760	07/17/2003	David L. Lewis	Mirus.030.09.2	9319

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/621,760	LEWIS ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5, and 9-20* is/are pending in the application.

4a) Of the above claim(s) *10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4 and 6-8 have been cancelled. Claims 10-20 have been withdrawn.

Claims 1-3, 5, and 9 are under examination.

Response to Arguments

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-3, 5, and 9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent No. 5,744,335, in view of both Boussif et al. (WO 01/59087) and Fire et al. (U.S. Patent

No. 6,506,559). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to (i) a deliverable composition comprising an amphipathic compound, polyvinylamine and siRNA (claim 1); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes and R1 and R2 are the same (claims 2 and 3), and (ii) a process for the *in vitro* delivering a siRNA to a mammalian cell (claims 5 and 9). The specification discloses that the amphipathic compound may be mixed with the polyvinylamine after the addition of siRNA (i.e., siRNA encapsulation by the amphipathic compound is not required for transfection) (p. 3, paragraph 0020).

The patent claims recite a process for transfecting a polynucleotide into a mammalian cell by delivering a composition comprising an amphipathic compound, a histone, and the polynucleotide, wherein encapsulation of the polynucleotide by the amphipathic compound is not required for transfection (claims 1 and 2), wherein the amphipathic compound is a 1,4 disubstituted piperazine and wherein the substituting groups are C6 to C24 alkenes (claims 6 and 7). The specification defines that R1 and R2 could be the same and the polynucleotide can be an antisense oligonucleotide (Summary of the invention, lines 54-67, column 7, lines 14-17). The patent claims do not recite polyvinylamine (PVA). Boussif et al. teach a method for introduction of antisense oligonucleotide into cells by using a composition comprising PVA, and amphipathic compound, and an antisense oligonucleotide (p. 4, last paragraph; p. 7, last paragraph; p. 8; p. 11, second to last paragraph; p. 12, last paragraph; p. 13; p. 21,

last paragraph, p. 22). Based on these teachings, one of skill in the art would have known that PVA is suitable to deliver antisense oligonucleotides to cells and would have found obvious to modify the patent claims by substituting the histone with PVA to achieve the predictable result of delivering antisense oligonucleotides to cells. The patent claims taken with Boussif et al. do not teach siRNA. Fire et al. teach that siRNAs are more efficient than antisense oligonucleotides (column 2, lines 10-20, column 3, lines 19-34, column 5, lines 14-30). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the patent claims by using siRNA to obtain the predictable result of inhibiting gene expression with high efficiency.

Thus, application claims and the patent claims are obvious variants.

The applicant argues that the 1.132 Declaration submitted by Applicants in response to the prior Office Action also applies to the double patenting rejection. The Declaration states that the cationic polymer, histone, plus the amphipathic compound and plasmid DNA from the cited '335 patent form an effective plasmid DNA delivery agent. However the cationic polymer from Boussif et al., polyvinylamine, plus the amphipathic compound and plasmid DNA does not form an effective plasmid DNA delivery agent. The data is provided.

Therefore, it could not have been obvious, at the time the invention was made, to substitute polyvinylamine for histone. In fact, the data shows that one having skill in the art would have been taught away from the substitution suggested in the Action. The only prior art at the time of the invention was delivery of large strands of DNA and

delivery components for assisting transfection of very short siRNA was unknown. "A prima facie case of obviousness can be rebutted if the applicant...can show that the art in any material respect 'taught away' from the claimed invention." In re Haruna, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001).

A person having skill in the art who considered the '335 patent in view of Boussif et al. and Fire et al. would not have gone through the exhaustive listing of every known polycation in Boussif et al., where polyvinylamine was not even used in the working examples, and substituted it for histone since, at the time, the prevailing knowledge was that polyvinylamine would not perform delivery.

The applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

As previously noted, the Declaration does not pertain to the instant rejection because the instant rejection is based on the delivery of antisense oligonucleotides and siRNA and not plasmids. The fact that the PVA of Boussif et al. and the amphipathic compound do not form an effective plasmid DNA delivery agent is not material to the instant rejection because plasmids are not used. The data in the Declaration does not teach away from the substitution suggested by the examiner because the substitution is for the delivery of siRNAs and not plasmids. To be persuasive, the data from the Declaration must indicate that the PVA and amphipathic compounds do not form an effective delivery agent for oligonucleotides and siRNA.

The applicant argues that the only prior art was delivery of large strands of DNA and that the delivery components for assisting the transfection of very short siRNA was unknown. This is not found persuasive. Boussif et al. teach PVA for assisting the transfection of very short nucleic acids such as antisense oligonucleotides. The fact that PVA was not used in the working examples of Boussif et al. does not take away from the fact their teaching that PVA is suitable for the delivery of short nucleic acids. Therefore, the knowledge in the prior art was that PVA would perform delivery of short nucleic acids. Based on these teachings, one of skill in the art would have known that PVA is suitable for the delivery of short nucleic acids and would have reasonably expected to be successful in using PVA to deliver siRNAs. Apart from arguments, the applicant did not provide any evidence to the contrary.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5, and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (WO 01/59087), in view of each Wolf et al. (US Patent 5,744,335), Bischoff et al. (U.S. Patent No. 6,291,423), and Fire et al. (U.S. Patent No. 6,506,559).

Boussif et al. teach a method for transfecting a mammalian cell *in vitro* by using a composition comprising an amphipathic compound, PVA and a nucleic acid such as an antisense oligonucleotide; the amphipathic compound greatly enhances transfection efficiency, i.e., facilitates oligonucleotide entry into the cell (claims 1, 5, and 9) (p. 4, last paragraph; p. 7, last paragraph; p. 8; p. 11, second to last paragraph; p. 12, last paragraph; p. 13; p. 21, last paragraph, p. 22). Boussif et al. teach that any natural or synthetic amphiphile used in the art for transfection purposes can be employed in their method (p. 14).

Although Boussif et al. teach that any amphiphile known to enhance transfection efficiency can be used, they do not specifically teach 1,4 disubstituted piperazines, wherein the substituting groups are identical C6 to C24 alkenes (claims 2 and 3). However, at the time the invention was made, 1,4 disubstituted piperazines were well known and used in the prior art in transfection methods (see Wolf et al., column 2, lines 6-14 and 40-67; column 9, lines 60-67; column 10, lines 45-55; Bischoff et al., Abstract; column 4, Formula III, column 10, line 56 through column 11, line 14). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Boussif et al. by substituting their amphipathic compound with the 1,4 disubstituted piperazines taught by the prior art to achieve the predictable result of obtaining a composition suitable for introducing oligonucleotides into cells.

Boussif et al., Wolf et al., and Bischoff et al. teach antisense oligonucleotides and not siRNA (claims 1 and 5). Fire et al. teach that siRNAs are more efficient than antisense oligonucleotides in inhibiting the expression of target genes (column 2, lines

10-20, column 3, lines 19-34, column 5, lines 14-30). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Boussif et al., Wolf et al., and Bischoff et al. teach by substituting their antisense oligonucleotide with a siRNA to achieve the predictable result of inhibiting gene expression with high efficiency.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant traversed the instant rejection on the grounds that the inventors of the '335 patent, Wolf et al., are also inventors in this application. They have supplied the 1.132 Declaration using data known at the time of filing for the delivery of plasmid DNA. Plasmid DNA was the DNA delivered in the referenced prior art and the significant differences between the delivery properties of plasmid DNA and siRNA were unknown at the time of filing this application. However, it was known by the inventors that the PVA did not perform delivery of the plasmid DNA described in Wolf et al. and Boussif et al.

A rejection under 35 U.S.C. 103(a) would be appropriate if a person of ordinary skill would have been motivated to modify a primary reference by deleting features thereof or by interchanging with or adding features from pertinent secondary references. However, the prohibition against destroying the function of the combination is inherent in the logic behind combining references to render a claimed invention obvious. If the proposed combination of the references so alters the primary reference that its broad

function can no longer be carried out, the combination of the prior art would not have been obvious to a designer of ordinary skill in the art.

The Declaration under 37 C.F.R. 1.132, that polyvinylamine/1,4- disubstituted piperazine/DNA complexes are not effective plasmid DNA transfection complexes. Conversely, histone/1,4-disubstituted piperazine/siRNA complexes are not effective siRNA transfection complexes. Therefore, histone and polyvinylamine have patentably distinct properties. Furthermore, while '335 teaches that histone/1,4-disubstituted piperazine may be an effective plasmid DNA transfection composition, the data in the declaration clearly show that histone/1,4-disubstituted piperazine is not an effective (siRNA) transfection reagent. Therefore, the finding that polyvinylamine/1,4-disubstituted piperazine does form an effective siRNA transfection composition must be considered to be an unexpected result.

The applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

The Declaration is not material to the instant rejection because the instant rejection is based on using PVA/piperazine/siRNA and not on using PVA/piperazine/ plasmid or histone/piperazine/siRNA. All that the data indicates is that PVA/piperazine is not efficient in delivering plasmids and that histone/piperazine is not efficient in delivering siRNA. The data is silent regarding the capacity of PVA/amphipathic compounds to deliver antisense oligonucleotides or siRNAs.

Boussif et al. teach PVA/amphipathic compound for the delivery of antisense oligonucleotides. Boussif et al. also teach that any amphipathic compound can be used in their composition (see the rejection above). Since the prior art teaches piperazine as an amphipathic compound suitable for nucleic acid delivery, it would have been obvious to one of skill in the art to modify the composition of Boussif et al. by replacing their amphipathic compound with the piperazine to obtain PVA/piperazine with the predictable result of obtaining a composition suitable for the delivery of antisense oligonucleotides. There is no indication from the data presented in the Declaration that piperazine would not work in the composition of Boussif et al. for the delivery of antisense oligonucleotides. And because Boussif et al. teach that PVA in conjunction with amphipathic compounds are effective to introduce antisense oligonucleotides into cells, the argument of unexpected result is not found persuasive. Antisense oligonucleotides and siRNAs are short nucleic acids and one of skill in the art would have expected that the composition of Boussif et al. or the modified version (i.e., PVA as the amphipathic compound) would also work for siRNAs. This is evidenced by the prior art, which teaches that compositions comprising polycations (such as made of monomers containing vinyl) and amphipathic compounds such as piperazine are effective in introducing siRNAs into cells (see Wolf, WO 03/040375, Abstract, p. 4, lines 14-30, p. 6, lines 8-20, p. 18, lines 9-14, p. 20, line 13; the reference is of record in Application 10/345,021 to which the instant application claims priority).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633